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MAKROCYCLISCHE CHELATE UND VERWENDUNGSVERFAHREN.
CHELATES MACROCYCLIQUES ET LEURS MODES D'UTILISATION.

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REF. NON-PATENT-LIT.: JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 110, no. 18, 31st August 1988, pages 6266-6267, American

Chemical Society; C.F. MEARES et al.: "The peptide way to macrocyclic bifunctional chelating agents: synthesis of 2-(p-nitrobenzyl)-1,4,7.10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid and study of its yttrium (III) complex"

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DETDEN. . . tetraacetic acid (EDTA), useful for binding metals other than copper, such as indium. These compounds are useful for imaging of **tumors**.

The usefulness of radionuclide materials in **cancer** therapy is disclosed in the article, Kozak et al., "Radionuclide-conjugated monoclonal antibodies: A Synthesis of Immunology, in Organic Chemistry and. . .

The . . . from the group consisting of hormones, steroids, enzymes, and proteins. These haptens are desirable because of their site

specificity to **tumors** and/or various organs of the body. The preferred hapten for use in treating cellular disorders or various disease conditions is. . .

An embodiment of the invention involves a **ligand-hapten conjugate** of formula II: <image> wherein X and R.sub1. to R.sub4. are as previously defined in formula I. This conjugate chelates. . . conjugate. The kinetics of the formation reactions for these compounds are so rapid that it is desirable to have the **ligand-hapten conjugate** available in the pharmacy immediately prior to use. The conjugate can then be mixed in the radionuclide to form a. . . subsequently, the metal chelate conjugate formed can be purified by, for example, size exclusion high pressure liquid chromatography. A desirable **hapten** for the **ligand conjugate** can be selected from the group consisting of hormones, steroids, enzymes, and proteins.

The . . . Q can be a monoclonal antibody, wherein the antibody is directed and created against an epitope found specifically on the **tumor** cells. Thus, when Pb.sup2..sup1..sup2. is transported to the antigen site and, subsequently, decays in secular equilibrium to Bi.sup2..sup1..sup2. and its. . . be easily reached within the 1 hour half-life of Bi.sup2..sup1..sup2.. It is also possible to use this method to treat **cancers**, where the cells are widely differentiated. This might be preferred where only a long-range beta-emitter, such as Y.sup9..sup0., is desired.. . .

The . . . diagnostic tool. Thus, when Pb.sup2..sup0..sup3. is linked by use of the chelate to a hapten, which specifically localizes in a **tumor**, then that particular localization can be three dimensionally mapped for diagnostic purposes in vivo by single photon emission tomography. Alternatively,. . .

The . . . to treat adult T-cell leukemia in mammals. T-cell leukemia is characterised by extraordinarily large amounts of IL-2 receptors on the **tumor** cells. The antibody localizes specifically to these **tumor** cells to deliver its radiation.

The . . . antibody B72.3, which binds specifically to a glycoprotein on LS-174T cells. This glycoprotein is also in humans who have colon **cancer**. The model system of this example is an athymic mouse, into which have been implanted LS-174T cells to develop a **tumor** on the flank of the animal where the cells were implanted. The diagnostic method used to visualize the growing **tumor** involves the following components. The chelate of compound 12 is first coupled to gadolinium or Pb.sup2..sup0..sup3. by mixture of the. . .

In . . . is injected or introduced into body fluids of a mammal. The gadolinium then localizes along with the antibody to the **tumor** and conventional resonance magnetic imaging techniques are used to visualize the **tumor**.

In . . . metal-labelled protein conjugate is similarly introduced into the mammal, but gamma camera or SPECT imaging is used to visualize the **tumor**.

CLMEN 13. A **ligand-hapten conjugate** of formula II: <image> where R.sub1. to R.sub4., and n are as defined in claim 1; and X' is as. . .